EDITORIAL

Mortality after myocardial infarction in patients with diabetes mellitus

Akhil Kapur, Rodney De Palma

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See article on page 1577

Diabetes mellitus (diabetes), in particular type 2 diabetes, constitutes one of the largest emerging threats to health in the 21st century. It is estimated that by 2030 as many as 360 million people world wide will be affected.[1]

The cause of death in those with diabetes is dominated by coronary heart disease, accompanied by increased rates of stroke and peripheral vascular disease: so called macrovascular complications. At least two-thirds of deaths are attributable to these cardiovascular diseases and their sequelae.[2] A true picture of the extent of macrovascular complications is obscured, however, by inaccurate death certification[3] and diagnostic criteria[4] based on the development of microvascular complications (retinopathy, neuropathy, nephropathy). The Euro Heart[5] Survey demonstrated that if one applied oral glucose tolerance tests to those presenting with all forms of acute coronary syndrome, two-thirds display impaired glucose regulation.

In the USA, although the overall mortality rate associated with coronary heart disease has declined over the past 20 years, this trend has not been reflected in a decline of mortality rates in patients with diabetes.[6] Results published in this issue of *Heart* from the Swedish registry on coronary care (RIKS-HIA) confirm this trend (***see article on page 1577***).[7] After a myocardial infarction (MI), patients with diabetes had an increased mortality rate compared with non-diabetic patients. Moreover, despite the existence of treatments which may benefit diabetic patients disproportionately, the relative hazard of mortality in diabetic patients has improved little compared with non-diabetic patients between the time periods 1995–8 and 1999–2002. These observations give us a glimpse of the vast epidemic that is approaching, if not upon us.

MORTALITY: WHAT DOES EPIDEMIOLOGY TELL US?

In the Multiple Risk Factor Intervention Trial (MRFIT), men with diabetes had a threefold higher absolute risk of cardiovascular death than non-diabetic men (160 vs 53 cardiovascular deaths per 10 000 person-years) even after controlling for age, race, income, cholesterol levels, blood pressure and smoking.[8]

The Framingham Study[9] 20-year follow-up similarly demonstrated that patients with diabetes not only had a higher mortality with their index event, they also had a higher incidence of reinfarction and heart failure in the acute and postinfarction periods.

The FINMONICA Study,[10] which looked at out-of-hospital deaths as well as deaths from index admission, showed that while diabetic women have a higher in-hospital and 1-year mortality, diabetic men have a higher overall mortality due to out-of-hospital death.

The risk of a first cardiovascular event in patients with diabetes is as high as in non-diabetic patients who have already had a cardiovascular event.[11] Guidelines reflect this concept by treating diabetes without overt coronary disease as a ''postinfarct'' equivalent.[12–14]

CORONARY ARTERIES: DIABETES IS DIFFERENT

Patients with diabetes have more multivessel, diffuse and distal coronary disease, smaller reference vessels, poorer coronary collateral circulation and more left main stem disease.[15–17] In a study more plaque ulceration and intracoronary thrombus was observed in diabetic arteries[18] than in those without diabetes. These features in combination with upregulated glycoprotein IIb/IIIa receptors, inflammation and endothelial dysfunction, make these patients particularly vulnerable to the atherosclerotic process and its sequelae.

ACUTE CORONARY SYNDROMES (ACS)

The risk

Diabetes doubles the risk for ACS with an additional doubling of the clinical risk once the event has occurred.[19–22] Among diabetic patients who have had an acute MI about half were not known to be diabetic at the time of presentation.[23] According to registry data, patients with diabetes present acutely more often with heart failure or non-ST elevation ACS than ST elevation MI.[24]

Management

Hyperglycaemia in the setting of an ACS is associated with poor outcome. The DIGAMI Study investigated intensive insulin treatment at the time of an index acute MI and for a minimum of 3 months.[25] They found an 11% absolute reduction in mortality at 1 year among those randomised to insulin. DIGAMI 2 investigated those with hyperglycaemia and overt type 2 diabetes using different glucose lowering

See end of article for authors' affiliations

Correspondence to: Dr A Kapur, Department of Cardiology, London Chest Hospital, Bonner Road, London E2 9JX, UK; akhil.kapur@bartsandthelondon.nhs.uk

Abbreviations: ACS, acute coronary syndrome(s); MI, myocardial infarction; PCI, percutaneous coronary intervention

regimens.[26] Glycaemic targets were not achieved and no difference in mortality was detected.

Diabetic patients benefit from prompt revascularisation in acute STEMI, both with fibrinolysis and primary percutaneous coronary intervention (PCI). The magnitude of benefit and access to reperfusion is greater with a primary PCI strategy.[27] A systematic review by Keeley *et al*[28] and also subgroup analysis data from PRAGUE-2[29] confirm that those with the highest risk, including those with diabetes, can achieve 30-day mortality rates of 7% with primary PCI compared with 23% for a similar group of patients receiving lysis.

Nevertheless, diabetes portends a higher mortality even if epicardial reperfusion is attained using either lysis[30] or PCI. Patients with a recurrent MI fare worse still than those with a first MI. The angioplasty substudy of GUSTO-IIb demonstrated that the incidence of multivessel disease among patients with diabetes is greater than in those without (45.3% vs 32.4%), mean ejection fraction was also lower. Death or reinfarction was higher in diabetic patients both at 30 days (13.1% vs 8.5%) and at 6 months (18.8% vs 11.4%,).[31]

Given the poor outcomes, contemporary guidelines also mandate early invasive investigation and interventional management of non-ST elevation ACS.[32] The FRISC II[33] study, again via subgroup analysis, demonstrated that diabetic patients with non-ST elevation ACS benefited from revascularisation using a composite end point of death and reinfarction.

The advent of the ''Heart Attack Centre'' strategy may provide an opportunity for aggressive interventional and medical management to reduce the excess mortality in diabetic patients further.

CONCLUSION: WHAT CAN BE DONE?

ACS are the most common presentation of coronary disease in patients with diabetes. Two-thirds of patients display glucometabolic disorders in the coronary care unit and in the cardiac catheter laboratory, patients with diabetes have worse disease than non-diabetic patients on initial presentation.

Identification

Underdiagnosis of diabetes is a manifest problem. Using fasting plasma glucose instead of oral glucose tolerance tests fails to detect 40–60% of those with dysglycaemia.

Cardiologists must help to identify these patients more accurately[34–36] with programmes to screen patients in clinic, in the coronary care unit and in the cardiac catheter laboratory. Conversely, greater cooperation between cardiologists and diabetologists to identify coronary disease in known diabetic patients will allow a fast track for coronary investigation and intervention in this group and enhance access to proven treatments which are underused in patients with diabetes.

Underuse of treatments

Although there is a consensus from trial data that diabetic patients constitute a high-risk group worthy of aggressive identification and management, observational registries paint a different picture. The findings of the GRACE[37] investigators provide an insight into ''real-world'' practice and are at odds with acknowledged guidelines. Their data suggest that there is an underuse of invasive investigation and percutaneous revascularisation in high-risk patients with ACS. The RIKS-HIA data in this issue of the journal also confirm the underuse of treatment in patients with diabetes.[7]

Risk modification works well in diabetic patients, as highlighted in a randomised controlled environment, where adherence to strict targets is maintained (STENO-2).[38] The RIKS-HIA data mirror that of revascularisation—namely, underprovision of secondary prevention treatments, notably statins, in diabetic patients. Contemporary data from the latest Euro Heart Survey demonstrate that this trend continues. Clearly there is a ''practice'' gap as well as a knowledge gap that needs to be bridged.

Dedicated studies: narrowing the gap

A valid criticism of our knowledge in managing such patients is that we are still reliant for the most part on substudies of clinical trials. To rectify this, a series of trials designed to investigate patients with diabetes and using cardiac outcome end points has begun. These may allow an improvement in existing treatments to narrow the gap and may even result in new treatments or strategies that may be beneficial in patients with diabetic coronary disease but not those with non-diabetic coronary disease. CARDS,[39] looking at primary prevention with a statin, is probably the first major contemporary study in this mould to have reported, and more trials dedicated to patients with diabetic coronary disease are on their way.

BARI 2D[40] is assessing revascularisation against aggressive medical treatment in diabetic patients. CARDia,[41] with recruitment now complete, is investigating the outcomes of symptomatic patients with multivessel or complex single-vessel disease randomised to contemporary PCI or surgical revascularisation. FREEDOM[42] is a larger but similar surgery versus PCI trial, recruiting globally.

It is therefore at an opportune moment that the comprehensive European Society of Cardiology Guidelines[43] on ''diabetes, prediabetes, and cardiovascular diseases'' have been published. Their clarion call to cardiologists and diabetologists to join forces to diagnose, prevent and treat glucometabolic disorders aggressively is an important message. Registry data like RIKS-HIA further remind us that ignoring the guidance may undo the progress in beneficial clinical outcomes achieved to date in patients with cardiovascular disease.

Authors' affiliations

Akhil Kapur, Rodney De Palma, London Chest Hospital, Barts and the London NHS Trust, London, UK

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REFERENCES

1 **Wild S**, Roglic G, Green A, *et al*. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;**27**:1047–53.
2 **Geiss LS**, Herman WH, Smith PJ. Mortality in non-insulin dependent diabetes. In: Harris M, eds. *Diabetes in America*, 2nd ed. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney diseases, 1995:233–55.
3 **McEwen LN**, Kim C, Haan M, the TRIAD Study Group, *et al*. Diabetes reporting as a cause of death: results from the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care* 2006;**29**:247–53.
4 **Anonymous**. The expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997;**20**:1183–97.
5 **Bartnik M**, Rydén L, Ferrari R, on behalf of the Euro Heart Survey investigators, *et al*. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004;**25**:1880–90.
6 **Gu K**, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999;**281**:1291–7.
7 **Norhammer A**, Lindbäck J, Rydén L, *et al*. Improved but still high short- and long-term mortality rates after myocardial infarction in patients with diabetes mellitus: a time-trend report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission. *Heart* 2007;**93**:1577–83.
8 **Stamler J**, Vaccaro O, Neaton JD, *et al*. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**:434–44.
9 **Kannel WB**, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. *JAMA* 1979;**241**:2035–58.
10 **Miettinen H**, Lehto S, Salomaa V, *et al*. Impact of diabetes on mortality after the first myocardial infarction: the FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 1998;**21**:69–75.
11 **Haffner SM**, Lehto S, Ronnemaa T, *et al*. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without previous myocardial infarction. *N Engl J Med* 1998;**339**:229–34.
12 **Anonymous**. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel or ATP III): executive summary of the

third report of the National Cholesterol Program (NCEP III). *JAMA* 2001;**285**:2486–97.
13 **Anonymous**. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 update. *Circulation* 2002;**106**:388.
14 **Anonymous**. Third Joint Task force of European and other Societies on Cardiovascular Disease prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Executive summary. *Eur Heart J* 2003;**24**:1601–10.
15 **Moussa I**, Moses J, Wang X. Why do the coronary vessels in diabetics appear to be angiographically small? [abstract]. *J Am Coll Cardiol*, 1999;**33**(Suppl A) 78A..
16 **Morris JJ**, Smith LR, Jones RH, *et al.* Influence of diabetes and mammary artery grafting on survival after coronary bypass. *Circulation* 1991;**84**:III275–84.
17 **Abaci A**, Oguzhan A, Kahraman S, *et al.* Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 1999;**99**:2239–42.
18 **Silva JA**, Escobar A, Collins JA, *et al.* Unstable angina: a comparison of angioscopic findings between diabetic and nondiabetic patients. *Circulation* 1995;**92**:1731–6.
19 **Aronson D**, Rayfield EJ, Chesebro JH. Mechanisms determining course and outcome of diabetic patients who have had acute myocardial infarction. *Ann Intern Med* 1997;**126**:296–306.
20 **Malmberg K**, Yusuf S, Gerstein HC, *et al.* Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organisation to Assess Strategies for Ischemic Syndromes. *Circulation* 2000;**102**:1014–9.
21 **McGuire DK**, Emanuelsson H, Granger CB, *et al.* Influence of diabetes mellitus on clinical outcomes across the spectrum of acute coronary syndromes. Gusto-IIb. *Eur Heart J* 2000;**21**:1750–8.
22 **Svensson AM**, McGuire DK, Abrahamsson P, *et al.* Association between hyper- and hypoglycemia and 2-year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J* 2005;**26**:1255–61.
23 **Norhammar A**, Ternerz A, Nilsson G, *et al.* Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002;**359**:2140–4.
24 **Abbott RD**, Donahue RP, Kannel WB, *et al.* The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. *JAMA* 1998;**260**:3456–60.
25 **Malmberg K**, Ryden L, Efendic S, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;**26**:57–65.
26 Malmberg K, Ryden L, Wedel H, *et al*, DIGAMI 2 investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;**26**:650–61.
27 **Hsu LF**, Mak KH, Lau KW, *et al.* Clinical outcomes of patients with diabetes mellitus and acute myocardial infarction treated with primary angioplasty or fibrinolysis. *Heart* 2002;**88**:260–5.
28 **Keeley EC**, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
29 **Widimsky P**, Budesinsky T, Vorac D, PRAGUE Study Group investigators, *et al.* Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. *Eur Heart J* 2003;**24**:94–104.
30 **Mak KH**, Moliterno DJ, Granger CB, *et al.* Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I investigators. *J Am Coll Cardiol* 1997;**30**:171–9.
31 **Hasdai D**, Granger CB, Srivatsa SS, *et al.* Diabetes mellitus and outcome after primary coronary angioplasty for acute myocardial infarction: lessons from the GUSTO-IIb Angioplasty Substudy. Global use of strategies to open occluded arteries in acute coronary syndromes. *J Am Coll Cardiol* 2000;**35**:1502–12.
32 **Silber S**, Albertsson P, Aviles FF, *et al.* Guidelines for percutaneous coronary interventions: the task force for percutaneous coronary interventions of the European Society of Cardiology. *Eur Heart J* 2005;**26**:804–47.
33 **Anonymous**. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease investigators. *Lancet* 1999;**354**:708–15.
34 **Bartnik M**, Ryden L, Malmberg K, *et al.* Oral glucose tolerance test is needed for appropriate classification of glucose regulation in patients with coronary artery disease: a report from the Euro Heart Survey on Diabetes and the Heart. *Heart* 2007;**93**:72–7.
35 **Bartnik M**, Malmberg K, Hamsten A, *et al.* Abnormal glucose tolerance—a common risk factor in patients with acute myocardial infarction in comparison with population-based controls. *J Intern Med* 2004;**256**:288–97.
36 **Nathan DM**, Davidson MB, DeForonzo RA, *et al.* Zinman impaired fasting glucose and impaired glucose tolerance-implications for care. *Diabetes Care* 2007;**30**:753–9.
37 **Fox KAA**, Anderson FA, Dabbous OH, *et al.* Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart* 2007;**93**:177–82.
38 **Gaede P**, Vedel P, Larsen N, *et al.* Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;**348**:383–93.
39 **Colhoun HM**, Betteridge DJ, Durrington PN, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**:685–96.
40 **Brooks MM**, Frye RL, Genuth S, *et al.* Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) Trial. *Am J Cardiol*, 2006;**97**:9–19G (Epub)..
41 **Kapur A**, Malik IS, Bagger JP, *et al.* The Coronary Artery Revascularisation in Diabetes (CARDia) trial: background, aims, and design. *Am Heart J* 2005;**149**:13–9.
42 **Anonymous**. National Heart, Lung, and Blood Institute (NHLBI). Comparison of Two Treatments for Multivessel Coronary Artery Disease in individuals with Diabetes (FREEDOM). Available at http://www.clinicaltrials.gov/ct/show/NCT00086450 (accessed 6 September 2007).
43 **Anonymous**. Guidelines on Diabetes, Prediabetes, and Cardiovascular Diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007;**28**:88–136.